REMARKS

Claims 1-6 and 8-15 are pending in this application. Claims 1-6 and 8-15 were variously rejected under 35 U.S.C. § 112, first paragraph, and were rejected under 35 U.S.C. § 112, second paragraph. Claims 1-4, 6, and 8-14 were rejected under 35 U.S.C. § 102(e). Claims 11-14 were rejected under 35 U.S.C. § 103.

By this amendment, claims 1 and 11 have been amended without prejudice or disclaimer of any previously claimed subject matter. Support for the amendments can be found, *inter alia*, throughout the specification, for example, at page 32, lines 8-10. The amendments are made solely to promote prosecution without prejudice or disclaimer of any previously claimed subject matter. With respect to all amendments and cancelled claims, Applicant has not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicant expressly reserves the right to pursue prosecution of any presently excluded subject matter or claim embodiments in one or more future continuation and/or divisional application(s).

Applicant has carefully considered the points raised in the Office Action and believe that the Examiner's concerns have been addressed as described herein, thereby placing this case into condition for allowance.

Rejections under 35 U.S.C. §112, first paragraph

Claims 1-6 and 8-15 were rejected under 35 U.S.C. §112, first paragraph, for allegedly not enabling any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention without undue experimentation. Claims 1-6 and 8-15 were rejected under 35 U.S.C. §112, first paragraph, for allegedly failing to comply with the written description requirement. Applicant respectfully traverses these rejections.

Enablement

The claimed invention is directed to a method of suppressing a respiratory syncytial virus (RSV) infection in an individual who has been exposed to RSV through administering, to the

respiratory tract of the individual, a composition comprising a polynucleotide comprising an immunostimulatory sequence (ISS). The ISS comprises the sequence 5'-CG-3' and the administered polynucleotide is greater than 6 and less than about 200 nucleotides in length. The composition is not administered in conjunction with RSV antigen, immunostimulatory cytokine, and non-nucleic acid adjuvant. The claimed invention is also directed to a kit for use in the claimed method.

The Examiner states that the disclosure does not "provide a working example where an ISS was used to suppress RSV infection in a human or similar animal model" and that the "teaching suppression of RSV infection in mice does not teach one skilled in the art how to suppress RSV infection in humans." Office Action, page 4. The Examiner also states that "the specification does not enable one skilled in the art to use any 5'-CG-3' ISS to suppress RSV infection in mice or humans." Office Action, page 5. The Examiner then concludes that it would require undue experimentation for one skilled in the art to make and use the claimed invention. Office Action, page 5. The Examiner's concerns essentially relate to the effective "scope" of enablement and whether the specification adequately supports and enables the method and ISS as claimed to one of skill in the art. Base on the following, Applicant respectfully submits that the Examiner's concerns regarding enablement are misplaced and unnecessary.

It appears as though the Examiner is asking that a particular immunostimulatory sequence demonstrate suppression of RSV infection in a human clinical trial in order to fulfill the enablement requirement for the claimed methods. Certainly, this is not a proper standard for enablement of this invention. The court has stated in both the pharmaceutical and medical device fields that "Title 35 does not demand that such human testing occur within the confines of Patent and Trademark Office (PTO) proceedings" and that FDA approval "is not a prerequisite for finding a compound useful within the meaning of the patent laws." *In re Brana*, 34 USPQ2d 1436 (Fed. Cir. 1995); *Scott v. Finney*, 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 (Fed. Cir. 1994).

Applicant respectfully points out that it is a well-established principle of patent law that "patent applicants are not required to disclose every species encompassed by their claims, even in

an unpredictable art." *In re Vaeck*, 947 F.2d 488, 496 (Fed. Cir. 1991). In *In re Angstadt*, the Court of Customs and Patent Appeals considered the issue of whether section 112 requires disclosure of a test with every species covered by a claim and concluded that requirement of such a complete disclosure would necessitate a patent application with thousands of examples and "would force an inventor seeking adequate patent protection to carry out a prohibitive number of actual experiments." *In re Angstadt*, 537 F.2d 498, 502 (CCPA 1976). The court concluded that such a requirement would be against public policy because it would have the effect of "depriving inventors of claims which adequately protect them and [would limit] them to claims which practically invite appropriation of the invention while avoiding infringement[, which would] inevitably [have] the effect of suppressing disclosure." Id. at 504. Based on the foregoing, Applicant is not required to disclose a test with every host covered by the claim.

MPEP §2164.02 states that an "*in vivo* animal model example in the specification, in effect, constitutes a "working example" if that example "correlates" with a disclosed or claimed method invention" and that ""[c]orrelation" as used herein refers to the relationship between *in vitro* or *in vivo* animal model assays and a disclosed or a claimed method of use." The same section of MPEP also states that "if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate." Applicant respectfully points out that the cotton rat model used in this application is an art-accepted model for the study of RSV infection.[1] Therefore, Applicant respectfully submits demonstration of the claimed method with this animal model is sufficient to enable the invention.

With regard to the state of the art, Applicant submits that immunostimulatory polynucleotides are well known in the art and respectfully notes that polynucleotides with immunostimulatory sequences active in cells of many mammalian species have been described in scientific literature, including the cells of humans, monkeys, chimpanzees, cows, swine, dogs, cats, rabbits, mice and rats. In particular, much has been described about ISS activity in human cells and

[1] See, for example, specification, page 8, line 27, to page 9, line 2; Wyde *et al.* (1995) *Pediatr. Res.* 38:543-550, abstract (of record).

immunostimulatory sequences active in human cells have been the subject of much scientific and patent literature. Thus, Applicant submits that the ISS art is more mature than the Examiner asserts.

The Examiner relies on the reference of Silverman[2] to support this enablement rejection. Silverman describes immunostimulatory DNA and its application to treating airway inflammation and asthma. Although Silverman notes that "effects of ISS-ODN on the immune system depend on the specific sequence, animal species, dose time course, and route of delivery, so generalizations must be made with care",[3] the claimed invention is no "generalization." The claimed invention calls for treatment of a specific individual (exposed to RSV), a specific virus (RSV), administration to a specific site (respiratory tract), and a polynucleotide of a specific length (>6 and <200 nucleotides) containing a specific ISS (5'-CG-3'). Silverman, and the references cited therein, describe many CG-containing sequences with immunostimulatory activity. Thus, Silverman does not support this rejection.

Applicant respectfully submits that the specification provides all the information required for one of skill in the art to make and use the method to suppress an RSV infection as claimed. The specification describes ISS-containing polynucleotides for use in the invention. See, for example, page 17, line 3 to page 20, line 24. The specification also describes how to make ISS-containing polynucleotides (for example, at page 20, line 25 to page 24, line 28) and how to test such polynucleotides for ISS activity (for example, at page 13, lines 9-16; and page 17, lines 3-10). In addition, the specification describes methods to determine whether a given ISS-containing polynucleotide comprising the sequence 5'-CG-3' exhibits a suppressing effect on RSV infection as claimed. See, for example, page 30, line 6 to page 35, line 28. Examples 1-3 exemplify administration of a composition comprising an ISS-containing polynucleotide with a 5'-CG-3' sequence to an animal and measurement of RSV titers in an RSV infected animal. An effective dosage that can be used for a given host and the effectiveness of a claimed ISS-containing polynucleotide with a 5'-CG-3' sequence can be determined using that described in the specification and the knowledge of one skilled in the art. Thus, the specification provides adequate guidance

[2] Silverman *et al.* , 2003, *Am. J. Respir.Cell Mol. Biol.* 28:645-647, cited in Office Action.
[3] Silverman, page 646, left column.

pertaining how to use the claimed polynucleotides comprising an ISS that a skilled artisan would be able to practice the invention without undue experimentation.

Fulfillment of the enablement requirement does not require that every embodiment of the invention be predictable. Rather, unpredictability is permitted, the level of unpredictability permitted depending on the level of guidance provided by the specification and the knowledge in the art. Applicant respectfully notes that the test for enablement is not whether a certain amount of experimentation is required to practice an invention, but rather whether the amount of experimentation is "undue." *In re Wands*, 858 F2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). Indeed, the court found in *In re Wands* the enablement requirement met even though 4 of 9 antibodies analyzed (44%) were found to have the claimed binding requirements and those successful 4 were produced in only 2 of 10 fusion experiments. "Since one embodiment is ... disclosed in the specification, along with the general manner in which its current range was ascertained, ... other permutations of the invention could be practiced by those skilled in the art without undue experimentation." *United States v. Telectronics, Inc.*, 857 F.2d. 788, 8 USPQ2d 1217 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989).

The court in *In re Wands*, *Supra*, found that the enablement requirement was satisfied by a "disclosure [that] provides considerable direction and guidance on how to practice [the] invention and presents working examples," in view of the fact that "[t]here was a high level of skill in the art at the time when the application was filed, and all of the methods needed to practice the invention were well known." *Id.* at 740. Applicant respectfully submits that the instant specification provides a reasonable amount of guidance to the skilled artisan with respect to the identification and testing of polynucleotide sequences with immunostimulatory activity and that the skilled artisan would be able to extend the teachings of the specification and the art to other immunostimulatory polynucleotides as claimed.

According to the Office, claims are not rejected as broader than the enabling disclosure under 35 U.S.C. §112 for noninclusion of limitations dealing with factors which must be presumed to be within the level of ordinary skill in the art; the claims need not recite such factors where one of

ordinary skill in the art to whom the specification and claims are directed would consider obvious. MPEP §2164.08. The court has stated that "Enablement is not precluded by the necessity for some experimentation such as routine screening ...". *In re Wands, Supra.* Applicant respectfully submits that varying the nucleic acid sequence of oligonucleotides and testing the oligonucleotides for immunostimulatory activity are well within the bounds of routine experimentation by one of skill in the art.

In addition, the Office has recently issued claims directed to methods of treating a mammal, a subject or an individual through administering an immunostimulatory or immunomodulatory polynucleotide comprising an ISS, wherein the ISS comprises the sequence 5'-CG-3'.[4] All of these patents have claimed priority dates much earlier than or within two months of the priority date of the instant application. The claims in these patents are supported with experiments in which a limited number of 5'-CG-3' containing oligonucleotides were tested for a particular activity or effect in a mouse model and, in some cases, on human cells in culture. Thus, in these cases, the Office has apparently deemed the state of the art such that the task of identifying nucleotides surrounding the core 5'-CG-3' motif as not an undue burden to the skilled artisan.

Thus, Applicant respectfully submits that the pending claims are in compliance with the enablement requirements and a *prima facie* case of lack of enablement has not been established.

Written Description

The written description requirement "may be satisfied if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure" and compliance with the requirement "is essentially a fact-based inquiry that will 'necessarily vary depending on the nature of the invention claimed.'" See *Amgen, Inc. v. Hoechst Marion Roussel, Inc. and Transkaryotic Therapies, Inc.*, USPQ 65 USPQ2d 1385 (Fed. Cir. 2003); *Enzo Biochem, Inc. v Gen-Probe, Inc.*, 63 USPQ2d 1609 (Fed. Cir. 2002).

[4] See, for example, U.S. Pat. Nos. 6,613,751, 6,552,006, 6,534,062 and 6,498,148.

To establish a *prima facie* case of lack of written description, the Examiner must present by a preponderance of evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined in the claims. A general allegation of "unpredictability in the art" is not a sufficient reason to support a rejection for lack of written description. MPEP §2163.04. The Examiner states that the specification "does not disclose how one skilled in the art may use any 5'-CG-3' ISS to suppress human RSV infection" and that [w]orking examples of a method having the scope of the claimed invention are also lacking." Office Action, pages 5-6. Applicant respectfully submits that these statements do not meet the burden for a *prima facie* case.

For the written description requirement, possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicants was in possession of the claimed invention. MPEP §2163.02. Working examples are not necessary to meet the written description requirement. Thus, the Examiner's statement regarding the working examples does not support this rejection.

The claimed invention is directed to a method of suppressing an RSV through administering a composition comprising an ISS-containing polynucleotide, where ISS comprises the sequence 5'-CG-3' and the administered polynucleotide is greater than 6 and less than about 200 nucleotides in length. Disclosed in the specification, and known in the art, are the structural characteristics of an ISS-containing polynucleotide as claimed such that a skilled artisan would recognize possession of the claimed invention. See, for example, pages 17-20 of the specification. Quoting from the Office's Written Description Requirement Guidelines, the court in *Enzo* stated that "the PTO has determined that the written description requirement can be met by "show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ... *i.e.*, complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and

structure, or some combination of such characteristics." Guidelines, 66 Fed. Reg. at 1106 (emphasis added)." *Enzo Biochem, Inc. v Gen-Probe, Inc., Supra.*

Applicant respectfully submits that the specification in combination with that known in the art provides a description of sufficient, relevant, identifying structural and functional characteristics of an ISS to adequately describe possession of the claimed genus to one skilled in the art. Thus, the pending claims are fully described in the specification as filed. Accordingly, Applicant respectfully submits that the written description requirement has been met.

In sum, Applicant submits that the pending claims fall within the subject matter that is enabled and described by the specification. Accordingly, Applicant respectfully requests reconsideration and withdrawal of the rejections under 35 U.S.C. §112, first paragraph.

Rejection under 35 U.S.C. §112, second paragraph

Claims 1-6 and 8-15 were rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Applicant respectfully traverses this rejection.

The Examiner states that "wherein RSV antigen is not administered in conjunction with the administration of said composition ..." is "indefinite because one skilled in the art would know whether administering the claimed ISS, and an adjuvant, through different compositions and at different times would constitute administering the ISS "in conjunction with" an antigen." Office Action, page 6. Applicant respectfully disagrees with this assessment. The specification clearly describes that the methods of the invention "entail administering an ISS-containing polynucleotide ... to an individual without administering a respiratory virus antigen" and that "respiratory virus antigen is not administered to the individual in conjunction with administration of an ISS (*i.e.*, is not administered in a separate administration at or about the time of administration of the ISS)." Specification, page 15, lines 2-13.

Applicant respectfully submits that the instant claims, including the phrase "in conjunction with," are sufficiently definite when considered in view of the specification and the understanding of those of skill in the art.

In view of the foregoing, Applicant respectfully requests reconsideration and withdrawal of the rejection under 35 U.S.C. §112, second paragraph.

Rejection under 35 U.S.C. §102(e)

Claims 1-4, 6, and 8-14 were rejected under 35 U.S.C. §102(e) as allegedly being anticipated by Davis *et al.* (U.S. Patent 6,406,705) (hereinafter "Davis"). Applicant respectfully traverses this rejection.

As noted herein, the claimed invention is directed to a method of suppressing an RSV infection in an individual who has been exposed to RSV comprising administering an ISS-containing polynucleotide composition in an amount sufficient to suppress an RSV infection. The polynucleotide is greater than six and less than about 200 nucleotides in length and the ISS comprises the sequence 5'-CG-3'. The composition is not administered in conjunction with RSV antigen, immunostimulatory cytokine, and non-nucleic acid adjuvant. The claimed invention is also directed to a kit for use in the claimed method.

Davis is directed to methods for inducing an antigen specific immune response and states that the method "includes the steps of administering to the subject in order to induce an antigen specific immune response an antigen and a combination of adjuvants, wherein the combination of adjuvants includes at least one oligonucleotide containing at least one unmethylated CpG dinucleotide and at least one non-nucleic acid adjuvant." Davis also states that the "CpG oligonucleotide and the non-nucleic acid adjuvant may be administered with any or all of the administrations of antigen" and then goes on to list various scenarios for the administration of the adjuvants with the antigen. See, Davis, col. 2, lines 18-42; emphasis added.

The Examiner quotes Davis as stating that "the Th1 response can be induced using CpG DNA *alone, or* in combination with a[n] ... adjuvant ..." and states that Davis "teaches administering an ISS without antigen, or any other adjuvant." Office Action, page 8. This excerpt takes Davis' comment out of context and is misleading as to Davis' invention. As noted above, Davis summarizes the invention as a method for inducing an antigen specific immune response through administration of an antigen and a combination of adjuvants. The paragraph at col. 2, line 55, to col. 3, line 6, describes different embodiments of the method, for example, "the combination of adjuvants is administered simultaneously" or "the combination of adjuvants is administered sequentially." In that paragraph, Davis states: "In another aspect, the same method is performed but the subject is an infant and the Th1 response can be induced using CpG DNA alone, or CpG DNA in combination with a non-nucleic acid adjuvant at the same or different site, at the same or different time." Emphasis added. In the context of this paragraph and the entire specification, the phrase "using CpG DNA alone" is referring to the use of CpG DNA as the sole adjuvant, not the administration of CpG DNA without administration of antigen.

Thus, Davis does not teach administration of an immunostimulatory polynucleotide without an antigen or without a non-nucleic acid adjuvant. Since Davis does not teach each and every element of the claim, the reference does not anticipate the claimed invention.

Applicant respectfully requests reconsideration and withdrawal of the rejection under 35 U.S.C. §102(e).

Rejection under 35 U.S.C. §103

Claims 11-14 were rejected under 35 U.S.C. §103 as allegedly unpatentable over Davis. Applicant respectfully traverses this rejection.

Claims 11-14 are directed to a kit for use in the method of the invention comprising a composition comprising an ISS-containing polynucleotide and instruction for administration of the composition to the respiratory tract of an individual. The polynucleotide is greater than six and less

than about 200 nucleotides in length and the ISS comprising the sequence 5'-CG-3'. The claimed kit does not contain RSV antigen, an immunostimulatory cytokine, or a non-nucleic acid adjuvant.

To establish a *prima facie* case of obviousness, the prior art reference (or references when combined) must teach or suggest all the claim limitations. Also, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. The teaching or suggestion to make the claimed combination must be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20USPQ2d 1438 (Fed. Cir. 1991); MPEP §2143.

As described above, Davis does not teach or suggest administration of ISS-containing polynucleotide greater than six and less than about 200 nucleotides in length without administration of RSV antigen for use in suppressing an RSV infection. Additionally, Davis does not teach or suggest producing a kit as claimed. Thus, Davis provides no teaching or suggestion of the claimed invention. Further, Applicant respectfully submits that there is no suggestion or motivation in Davis to modify the teachings therein to arrive at the claimed invention.

Thus, Applicant respectfully submits that a *prima facie* case of obviousness has not been established with regard to claims 11-14.

Applicant respectfully requests reconsideration and withd rawal of the rejections under 35 U.S.C. §103.

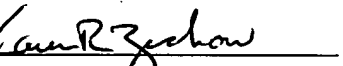
CONCLUSION

Applicant believes that all issues raised in the Office Action have been properly addressed in this response. Accordingly, reconsideration and allowance of the pending claims is respectfully requested. If the Examiner feels that a telephone interview would serve to facilitate resolution of any outstanding issues, the Examiner is encouraged to contact Applicant's representative at the telephone number below.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicant petitions for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 377882000900. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: April 28, 2005

Respectfully submitted,

By 

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